REMARKS

Reconsideration is respectfully requested. Claims 1 and 19 have been amended. Claims 2, 5, 7-18, and 22-30 were previously canceled. Claims 3, 20, 32-35, 37 and 40-55 have been canceled in this amendment without prejudice to filing these claims or similar claims in one or more divisional or continuation applications. On entry of this amendment, claims 1, 4, 6, 19, 21, 31, 36 and 38-39 will be pending for examination.

Status of the claims

Applicants thank the Examiner for entry of the amendment submitted on September 10, 2004 and for issuing a second non-final Office Action. Applicants acknowledge, with traverse, the Examiner's finding that claims 52-55, submitted in the previous response, are directed toward a nonelected invention. Applicants further acknowledge the Examiner's statement that claims 32-35 and 40-51 stand withdrawn from further consideration as being directed toward a nonelected invention. These claims have been canceled in this response without prejudice. Applicants reserve the right to file one or more divisional or continuation applications directed to the canceled claims.

Information Disclosure Statement

Applicants thank the Examiner for entry into the file and consideration of the information disclosure statements filed on November 11, 2004, January 7, 2005, and February 18, 2005. Applicants submit a Supplemental Information Disclosure Statement in the present application for the Examiner's consideration. Applicants request that the Examiner consider the cited references in light of the pending claims.

Rejections under 35 U.S.C. § 103(a)

As a preliminary matter, Applicants thank the Examiner for the withdrawal of the rejection of claims 1, 3, 4, 6, 19-21, 31, and 36-39 under 35 U.S.C. § 103(a) as being unpatentable over Bolognesi et al. (1996) in view of Krantz et al. (2000) from the previous Office Action.

In the current Office Action, the Examiner has rejected claims 1, 3, 4, 6, 19-21, 31, and 36-39 under 35 U.S.C. § 103(a) as being unpatentable over Bolognesi et al. (1996) in view of Tolman (1993).

Amended claims 1 and 19 are now limited to a peptide with a maleimide group which is covalently bonded to cysteine 34 of serum albumin, where the ratio of peptide to serum albumin is 1:1. Support for this amendment is found on page 10, paragraph 1, and page 27, line 9 and 17 of the specification as filed. The relevant sections are reproduced here:

> "Mobile blood components include serum albumin, transferrin, ferritin, and immunoglobulins such s IgM and IgG."
>
> "...peptide-maleimide-albumin conjugates will tend to comprise approximately a 1:1 molar ratio of peptide to albumin."
>
> "The single free thiol group of albumin, highly conserved among species, is located at amino acid residue 34 (Cys^{34})."

Specifically, 1) none of the cited references teach or suggest all the claim limitations, 2) the prior art combined with general knowledge fails to include a suggestion or incentive to modify the references, and 3) the references fail to teach that the modification would have a reasonable chance of success.

First, the cited prior art references fail to teach all elements of the claimed invention as amended. Claims 1, 4, 6, 19, 21, 31, 36, 38 and 39 have been amended to recite that the "peptide is covalently bonded to cysteine 34 of serum albumin." Bolognesi, et al. disclose HIV derived peptide sequences, and Tolman, et al. disclose the preparation of an HIV vaccine by creating a "co-conjugate" between antigenic cyclic peptides and a bacterial carrier protein, OMPC. Neither Bolognesi, et al. nor Tolman, et al. teach or suggest a peptide covalently bonded to cysteine 34 of serum albumin.

The references, in combination, thus fail to teach all elements of the claimed invention

Second, the references, separately or in combination, fail to provide the requisite motivation to combine their teachings to make the claimed invention. Specifically, none of the references cited by the Examiner provides one of ordinary skill in the art with motivation to conjugate HIV derived peptide sequences with a cysteine 34 of serum albumin.

Bolognesi, et al. fail to provide the requisite motivation to combine, as they simply disclose HIV derived peptide sequences, with no suggestion or motivation to conjugate to anything at all. Similarly, Tolman, et al. fail to provide the requisite motivation to combine, as they do not teach or suggest the coupling of an HIV derived peptide to cysteine 34 of serum albumin. Instead, Tolman, et al. teach conjugation to one specific bacterial protein, OMPC, for use as a vaccine. The conjugation of peptide sequences to carrier proteins such as OMPC for vaccine production is a common technique employed to promote development of an immune response by a host. Bacterial proteins are utilized because they are different than the host's blood components and will facilitate generation of an immune response. As such, the bacterial protein OMPC in Tolman, et al. was specifically chosen because it is different than blood components and would therefore facilitate generation of an immune response. In contrast, in the present invention, HIV peptides are conjugated to serum albumin *in vivo* or *ex vivo* to increase the half life of the HIV peptides while minimizing any immune response. When conjugated *ex vivo*, serum albumin would generally not be expected to elicit an immune response because it is highly similar if not identical to the endogenous protein; when conjugated *in vivo*, serum albumin is the endogenous protein and would not be expected to elicit an immune response. As such, in the present invention, the HIV peptides are conjugated to serum albumin rather than to the bacterial protein of Tolman, et al. in order to minimize any immune response of the conjugate upon its formation in a host or introduction into a host. Tolman, et al. teach away from the use of serum albumin.

Because the bacterial protein of Tolman, et al. and the serum albumin of the present invention are used for completely different purposes, neither Tolman et al. or Bolognesi, et al. provide the requisite motivation to conjugate HIV peptides to serum albumin in order to increase the half-life of HIV derived peptides while minimizing an immune response.

Third, the combined prior art teachings provide no reasonable expectation that the combination will succeed.

Nothing in the two references cited by the Examiner suggests that one of ordinary skill in the art would have a reasonable expectation of success in producing the claimed invention (an HIV peptide conjugated to a cysteine 34 of serum albumin). Combining the teachings of Tolman. et al. and Bolognesi, et al. would produce a peptide-bacterial protein conjugate for generating an immune response, not a peptide that retains its therapeutic activity with an increased *in vivo* half life while minimizing an immune response. As such, there is no expectation of success in combining the references cited by the Examiner in producing the claimed invention.

In view of the claim amendments and the foregoing arguments, Applicants request that the rejection under 35 U.S.C. §103 be withdrawn.

Patrick et al. (1987)

In a related case (Application No. 09/623,533) the Examiner rejected the pending claims under 35 U.S.C. §103 over the combination of Bolognesi et al., Tolman and Patrick et al, 1987. Applicants submit a copy of Patrick, et al. herewith in an Information Disclosure Statement for the Examiner's consideration.

While the Examiner has not yet rejected the claims over the combination of Bolognesi et al., Tolman and Patrick et al, 1987, Applicants wish to point out that none of the references cited by the Examiner, alone or together with Patrick et al., disclose or suggest the covalent bonding of a peptide to cysteine 34 of serum albumin in a 1:1 ratio of peptide to serum albumin. Instead, the

references disclose conventional conjugation methods that produce conjugates with several molecules of active agent coupled to each molecule of carrier. As such, these conventional conjugation methods produce a heterogeneous pool of conjugates at various ratios of molecule to carrier. In contrast, in the presently claimed invention, the conjugate is a 1:1 ratio of molecule (peptide) to carrier (serum albumin) where the peptide is specifically bonded to cysteine 34 of serum albumin.

Patrick et al. disclose a vaccine that can be made with BSA (Bovine Serum Albumin) as a carrier. Patrick et al. disclose "using standard techniques with a bifunctional conjugating agent such as carbodiimide, glutaraldehyde or bis-diazotized benzidine." (see col. 16, lines 10-15 of Patrick, et al.). These bifunctional conjugating agents react with amines, not with thiol groups. The bifunctional agents of Patrick, et al. provide conjugates where the peptides are attached at non-specific sites on the BSA.

The differences between the claimed invention and the techniques of the prior art including Patrick, et al. are outlined in the present specification as filed on page 28, lines 3-6, which provides:

> "Another advantage of peptide-maleimide-albumin conjugates is the reproducibility associated with the 1:1 loading of peptide to albumin specifically at Cys34. Other techniques, such as glutaraldehyde, DCC, EDC and other chemical activations of, e.g., free amines, lack this selectivity."

Patrick, et al. disclose the creation of a vaccine by conjugation of a peptide to an immunogenic carrier molecule. Column 16, line 26 of Patrick et al. provides "[t]he result of this conjugation reaction will be a mixture of synthetic proteins of the invention, each involving a different number of molecules of synthetic peptide conjugated per molecule of carrier protein." In contrast the claims of the present invention are directed to peptides that are specifically conjugated via a maleimide group to cysteine 34 of serum albumin, resulting in a 1:1 ratio of peptide to serum albumin.

There is no suggestion or motivation to modify the references or to combine the reference teachings to produce the claimed inventions as none of the references, either alone or together, teach or suggest conjugation of a peptide via a maleimide group to cysteine 34 of serum albumin, resulting in a 1:1 ratio of peptide to serum albumin. The references do not teach or suggest all claim limitations. As such, there is no reasonable expectation of success.

The claims are non-obvious over the combination of Bolognesi et al, Tolman and Patrick et al, 1987. As such, a rejection of the pending claims under 35 U.S.C. §103 would be improper.

Non-statutory double patenting rejection

The Examiner has rejected claims 1, 3, 4, 6, 19-21, 31, and 36-39 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6,107,489 (Krantz et al.) in view of Bolgnesi et al. (1996). In making this rejection, the Examiner supports his argument by alleging that "it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to modify the antiviral peptides described by Bolognesi et al. to include succinimidyl- or maleimido-containing reactive groups, as described by Krantz et al. (2000), that are capable of forming stable covalent bonds with blood components."

Applicants respectfully disagree with the Examiner's analysis and conclusion regarding obviousness in connection with this double patenting rejection. However, in order to expedite prosecution in this case, a terminal disclaimer is enclosed herewith to terminally disclaim the term of the patent that issues based upon this patent application with the patent term of U.S. Patent No. 6,107,489. In light of this, applicants respectfully request that the rejection of claims 1, 3, 4, 6, 19-21, 31, and 36-39 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6,107,489 (Krantz et al.) be withdrawn

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. **500862001500**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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